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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,202	09/29/2000	David Bar-Or	4172-3	3734

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/678,202	BAR-OR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-11 and 21-31* is/are rejected.

7)☒ Claim(s) *2-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 12 (filed 8/4/03), claims 32-58 have been cancelled.

Applicants' various species elections are acknowledged.

Applicants have traversed the restriction between subgenera G1 and G2. Applicants have argued that based on this restriction, two patents could issue with identical claims. However, applicants are not correct. Inventions within "G1" are subgeneric to the instant claims; they are by no means equivalent. For example, applicants could, in principle, amend the claims (after the first action on the merits) to claim a method of reducing the damage caused by ROS to cardiac tissue comprising the step of administering one of the following peptides. Applicants could then present a genus of 1000 or more specific sequences, and impose upon the examiner the burden of searching all 1000 (or more) specific sequences. If such an event were to come to pass, the examiner could argue that those 1000 specific sequences belong within the scope of G1 (assuming that none of them had been presented initially). On the other hand, if the claims are found allowable in their present form, or in further limited form, then any peptide sequences that might be encompassed by the claims will still be encompassed when the patent issues.

As it happens, the restriction between G1 and G2 will not be enforced if information is not "extracted out" from the references an put into the claims. If the claims are allowable in their present form, they will necessarily encompass anything that is subgeneric thereto. And if the claims become allowable with significant limitations introduced therein, it will

still be true that the claims will encompass any inventions that are subgeneric to the claims. Applicants will not be required to go through each of the references (cited in the specification) and exclude all embodiments (from the claims) which are disclosed in those references.

The (latent) restriction is maintained at the present time.

Claims 12-20 are withdrawn from consideration, since they do not encompass the elected specie.

The abbreviation "ROS" hereinbelow refers to "reactive oxygen species".

*

The specification is objected to.

- On page 6, line 7, a "web" address is provided. The contents are transient, and as such, reference to this address should be eliminated from the disclosure.
- There is an error in Figs 1A - 1D. Double bonds are missing from the imidazole group.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art

to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 27 recites that the peptide is administered "prophylactically". It is unclear as to the full scope of what may be encompassed by this, although that is not the point of this rejection. One interpretation is that claim 27 is asserting that disease can be prevented, or that the likelihood of, or incidence of disease can be reduced. If so, claim 27 lacks enablement. Another interpretation is that claim 27 is asserting that the damage caused by ROS on a given day can be reduced even if the peptide is administered to an animal several days earlier. According to this interpretation claim 27 also lacks enablement. Perhaps the peptides can mitigate damage caused by ROS while the peptides are still present in the body. But claim 27 encompasses the possibility of achieving meaningful reduction of damage even after the peptide has been metabolized.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, one cannot predict efficacy in the treatment of disease based on the disclosed experiments, and one cannot predict reduction in the damage caused by ROS after the peptide has been eliminated from

the body. Accordingly, "undue experimentation" would be required to practice the invention of claim 27.

*

Claim 27 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites that the peptide is administered "prophylactically". It is unclear as to the full scope of what may be encompassed by this. The Webster's Dictionary defines "prophylactic" as follows: (1) guarding from or preventing disease; or (2) tending to prevent or ward off. Given the dependence of claim 27 on claim 1, it is unclear what claim 27 encompasses. It is not clear how the directives of claim 1 are to be reconciled with those of claim 27. Claim 1 requires only that the damage done by "ROS" is "reduced". The first point is that caim 1 makes no mention of disease. The second point is that, if the objective is to "prevent" or "ward off" something, exactly what is it that is being prevented or "warded off"...? If the process or entity that is being prevented or "warded off" is a disease, then the claim dependence is not proper, since there is no suggestion in claim 1 that a disease can or should be prevented or "warded off". Another interpretation is that it is the "damage" done by ROS that is intended to be prevented or warded off. If this is the intended invention (of claim 27), then a question of timing arises. Suppose that there are two genetically identical rats (a "first" rat and a "second" rat), and on "day 1" of a study, a

peptide (according to claim 1) is administered to one of the rats. On day 3 of the study, ROS are formed in both rats and cause "damage". Is it the case that the peptide which was administered on day 1 is targeting ROS which did not exist at all on day 1...? One option would be to write claim 27 in independent form, so that it can be determined what is intended.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1 and 8-11 are rejected under 35 U.S.C. §103 as being unpatentable over Dunphy (*Am J. Physiol* **276**, H1591-1598, 1999) in view of Carter (USP 5,780,594).

Dunphy discloses that albumin reduces the damage done by reactive oxygen species. Dunphy does not disclose that the third amino acid from the N-terminus is histidine.

Carter discloses that SEQ ID NO: 3 (cols 9-10) is the sequence of human albumin. As is evident, the N-terminal peptide is D-A-H-K, which coincide with SEQ ID NO: 1 of the instant application.

Thus, it would have been obvious to one of ordinary skill that a peptide which conforms with the formula P1-P2 is effective to reduce the damage done by reactive oxygen species.

[Claims 9-11 are rejected because of the term "having" in line 3 of claim 1].

*

Claims 1, 8-11 and 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Gutteridge (*Biochim Biophys Acta* 759, 38, 1983) in view of Carter (USP 5,780,594).

Gutteridge discloses that albumin reduces the damage done by reactive oxygen species. Gutteridge does not disclose that the third amino acid from the N-terminus is histidine. Carter discloses that SEQ ID NO: 3 (cols 9-10) is the sequence of human albumin. As is evident, the N-terminal peptide is D-A-H-K, which coincide with SEQ ID NO: 1 of the instant application.

Thus, it would have been obvious to one of ordinary skill that a peptide which conforms with the formula P1-P2 is effective to reduce the damage done by reactive oxygen species.

[Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders].

*

Claim 1 is rejected under 35 U.S.C. §103 as being unpatentable over Halliwell (*Arch. Biochem Biophys* 246, 501, 1986).

Halliwell discloses, or at least implies, that SOD and catalase reduce the damage done by "ROS". Halliwell does not disclose that SOD and catalase both contain histidines.

Claim 1 has been amended to recite that "Xaa1 is the N-terminal amino acid of the peptide". However, this does not necessarily mean that the third amino acid from the N-terminus must be histidine. Much depends on what exactly "the peptide" (claim 1, line 9) is referring to. One interpretation is that "the peptide" refers to the peptide that is administered to the animal. According to this interpretation, a rejection would not be valid unless the reference (or combination of references) disclosed that there is, indeed, a histidine present 3 amino acids from the N-terminus. But there is another interpretation, and that is that "the peptide" refers to the peptide as defined by "P_1-P_2". According to this interpretation, the claim encompasses the possibility of the histidine being present at virtually any position in the peptide (the peptide, that is, which is administered to the animal). This is because of the term "having". If one begins with a peptide in which histidine is the third amino acid from the N-terminus, and adds several amino acids to the N-terminus, the histidine is no longer the third amino acid from the N-terminus. Accordingly, claim 1 encompasses the use of any histidine-containing peptide.

Thus, the claim is rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Ueda (*J Inorg Biochem* 55, 123, 1994).

Ueda discloses that the tripeptide Gly-Gly-His mimics the effect of SOD in dismuting superoxide. Also disclosed (page 123) is that H_2O_2 is converted to water and O_2 by catalase.

Thus, it would have been obvious to one of ordinary skill that Gly-Gly-His is effective to "scavenge" at least one reactive oxygen specie. The argument could stop here and be sufficient. In addition, it would have been obvious that by contacting a combination of Cu(II)-Gly-Gly-His and catalase with superoxide, the formation of ROS will be decreased, and hence the damage done be ROS will be reduced. [The instant claims do not preclude the simultaneous administration of multiple agents].

Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders.

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Das (*Meth Enzymol* 233, 601, 1994) in view of Satoh (USP 5051406) further in view of Carter (USP 5,780,594).

Das discloses that antioxidants such as tocopherol can be used to reduce the damage done

by "ROS". Das does not suggest combining the antioxidants with albumin. Satoh discloses that by combining drugs with albumin, improved results are obtained. Tocopherol is also specifically mentioned (see, e.g., figure 4). Satoh does not disclose that in albumin, histidine is the third amino acid from the N-terminus. Carter discloses that in albumin, histidine is the third amino acid from the N-terminus.

Thus, it would have been obvious that by combining an antioxidant such as tocopherol with albumin, the practioner would be meeting both of the following objectives:

(a) administration of a "first" agent which inhibits damage caused by ROS, and

(b) administration of a "second" agent which contains a histidine at the requisite position.

The claims do not preclude administration of multiple agents. [Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders].

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Kimoto (*Cancer Research* 43, 824, 1983) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Kimoto in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995).

Kimoto discloses a process which "comprises" administration of the peptide Gly-Gly-His,

with the result that growth of tumor cells is inhibited. Kimoto does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species.

One of ordinary skill would have expected that by administering the peptide Gly-Gly-His to a tumor-bearing mammal, reduction of tumor volumes can be achieved. Claim 1 requires that the damage caused by ROS be mitigated in some way. In this case, the "damage" is proliferation of tumor cells. By inhibiting the proliferation of tumor cells, the "damage" caused by ROS will be mitigated. [Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders].

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Konishi (USP 4,461,724).

Konishi discloses the use of peptides for treating ulcers. The peptides contain a histidine residue which is located 3 amino acids from the N-terminus, as required of the instant claims. Konishi does not disclose that the symptoms of ulcers are mediated by "ROS".

Structurally, the peptides of Konishi meet the requirements of the instant claims. The instant claims require that the damage caused by ROS be mitigated in some way. As it

happens, at least some of the "damage" observed in patients stricken with ulcers is caused by ROS. Whether ROS accounts for 10% of the damage or 80% of the damage or 1% of the damage makes little difference with regard to the validity of this rejection. The point is that if the Konishi compounds are indeed effective to reduce the tissue damage (or other damage) caused by ulcers, then the Konishi compounds must also be effective to mitigate the damage caused by ROS. Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Pickart (USP 5118665); or Pickart in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995); or Pickart in view of Roth (*Acta Chirugica Hungarica* **36**, 302, 1997)

Pickart discloses (e.g., col 18, table 3) that the peptide Gly-Lys-His exhibits SOD activity when complexed to manganese, and further, that the peptide is an antioxidant and can be used to treat inflammatory disorders. Knight discloses that the damage which accompanies inflammation is caused at least in part by "ROS". Roth also discloses that the damage which accompanies inflammation is caused at least in part by "ROS".

Thus, it would have been obvious to one of ordinary skill that by administering the peptide Gly-Lys-His (together with manganese) to a mammal, damage caused by ROS can be

mitigated.

Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders.

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Koyama (USP 5591711).

Koyama discloses the use of Gly-Lys-His for wound healing. Koyama does not disclose that, once tissue is wounded, further damage to that tissue is caused at least in part by "ROS".

Structurally, the peptides of Koyama meet the requirements of the instant claims. The instant claims require that the damage caused by ROS be mitigated in some way. As it happens, at least some of the "damage" inflicted upon wounded tissue is caused by ROS. If the Koyama peptides are indeed effective to promote wound healing, then at least some of the "damage" caused by ROS will be mitigated.

Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders.

Thus, the claims are rendered obvious.

*

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Kimoto (*Cancer Research* 43, 824, 1983) or Konishi (USP 4,461,724) or Pickart (USP 5,118,665) in view of Ames (*Proc Natl Acad Sci* **90**, 7915, 1993).

The teachings of the primary references are indicated above. Ames discloses that various diseases are mediated by ROS, and further, that antioxidants can be used to mitigate the damage caused by the ROS. Ames does not disclose the use of peptides which contain a histidine at the third position from the N-terminus.

[Claims 21-26, 28-31 are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders].

Thus, it would have been obvious that by administering an antioxidant peptide (as disclosed in one of the primary references) to an animal afflicted with a ROS-mediated disorder, the damage caused by the ROS can be mitigated.

*

- Reference 1 on the IDS (received 7/6/01) was stricken from the IDS because of the absence of a translation. If a translation is not available, it is suggested that the following be listed on the "other art" section of the IDS:

  Abstract of JP-62116565

- Reference 7 on the IDS (received 1/25/02) was stricken from the IDS because the citation is incomplete. For example, neither the author of the book, nor the year of publication, nor the publisher has been indicated.

- Reference 84 on the IDS (Adman) was stricken from the IDS because it was not received.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600